

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
27 June 2002 (27.06.2002)

PCT

(10) International Publication Number  
**WO 02/49616 A1**

(51) International Patent Classification<sup>7</sup>: A61K 9/12, 47/26

(21) International Application Number: PCT/SE01/02853

(22) International Filing Date:  
19 December 2001 (19.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0004750-6 19 December 2000 (19.12.2000) SE

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declaration under Rule 4.17:**

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL; AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

**Published:**

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/49616 A1

(54) Title: PHARMACEUTICAL AEROSOL FORMULATION

(57) Abstract: The invention relates to a pharmaceutical aerosol formulation comprising a surfactant that is an alkyl-polyglycoside of formula I, wherein DP is the average degree of polymerisation and has a value of from 1 to 4, and R is an alkyl chain or a mixture of alkyl chains having a chain length of from 6 to 22 carbon atoms; or a derivative thereof for the administration of a medicament for inhalation.

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**Example 3:**

Beclomethasone dipropionate B.P (SICOR) was weighed (0.2 g) into a 30 ml glass vial and 20 ml of surfactant solution in water ( $C_{10-12}$  d.p. 1.4, 0.8 g/l) added. The resultant suspension was incubated in a shaking bath at 25°C for three hours, to allow adsorption of the surfactant to the surface of the drug, and to give a drug-surfactant ratio of 10 mg surfactant/g drug. The suspension was then centrifuged (15,000 rpm, 20 minutes) and the particles of drug-surfactant were separated from the supernatant and dried in an oven at 50°C for at least 24 hours. The formulation was prepared as described in the preparation paragraph, with the following concentrations:

Beclomethasone dipropionate +  $C_{10-12}$  d.p. 1.4: 0.2%  
HFA-134a: to 100%

**Example 4:**

Beclomethasone dipropionate B.P (SICOR) was weighed (0.2 g) into a 30 ml glass vial and 20 ml of surfactant solution in water ( $C_{10-12}$  d.p. 1.4, 0.8 g/l) added. The resultant suspension was incubated in a shaking bath at 25°C for three hours, to allow adsorption of the surfactant to the surface of the drug, and to give a drug-surfactant ratio of 10 mg surfactant/g drug. The suspension was then centrifuged (15,000 rpm, 20 minutes) and the particles of drug-surfactant were separated from the supernatant and dried in oven at 50°C for at least 24 hours. The formulation was prepared as described in the preparation paragraph, with the following concentrations:

BDP  $C_{10-12}$  d.p. 1.4: 0.2%  
HFA-227ea: to 100%

**Example 5:**

Microparticles of salbutamol sulphate- $C_{12-14}$  d.p. 1.4 were prepared by spray drying from solution in water using a Büchi 190 mini spray drier fitted with a 7 mm pneumatic nozzle. A 10% w/v salbutamol sulphate in a solution of 0.06 g/l of  $C_{12-14}$  d.p. 1.4 was spray dried. The conditions and spray drying parameters were: pump speed, 5 ml min<sup>-1</sup>; air flow rate, 800 l h<sup>-1</sup>; aspirator level, 5; inlet temperature, 150°C ( $\pm 5^\circ\text{C}$ ) and outlet temperature 80°C ( $\pm 5^\circ\text{C}$ ). The material was desiccated immediately after drying. The formulation was prepared as described in the preparation paragraph, with the following concentrations:

Spray dried (SD) salbutamol sulphate +  $C_{12-14}$  d.p. 1.4: 0.08%  
HFA-134a: to 100%

**Example 6:**

Microparticles of salbutamol sulphate-C<sub>12</sub>G<sub>2</sub> were prepared by spray drying from solution in water using a Büchi 190 mini spray drier fitted with a 7 mm pneumatic nozzle. A 10% w/v salbutamol sulphate in a solution of 0.08 g/l of C<sub>12</sub>G<sub>2</sub> was spray dried. The conditions and spray drying parameters were: pump speed, 5 ml min<sup>-1</sup>; air flow rate, 800 l h<sup>-1</sup>; aspirator level, 5; inlet temperature, 150°C (± 5°C) and outlet temperature 80°C (± 5°C). The material was desiccated immediately after drying. The formulation was prepared as described in the preparation paragraph, with the following concentrations:

SD salbutamol sulphate + C<sub>12</sub>G<sub>2</sub>: 0.08%

HFA-134a: to 100%

**Example 7:**

Salbutamol sulphate was weighed (0.2 g) into a 30 ml glass vial and 20 ml of surfactant solution in CH<sub>2</sub>Cl<sub>2</sub> (C<sub>14</sub> d.p. 1.4, 0.6 g/l) added. The resultant suspension was incubated in a shaking bath at 25°C for three hours, to allow adsorption of the surfactant to the surface. This was then filtered under vacuum and the particles of drug-surfactant collected and dried overnight at room temperature. The formulation was prepared as described in the preparation paragraph, with the following concentrations:

Salbutamol sulphate + C<sub>14</sub> d.p. 1.4: 0.08%

HFA-134a: to 100%

7

**Control 1:**

The formulation was prepared as described in the preparation paragraph, with the following concentrations:

Beclomethasone dipropionate: 0.2%

HFA-134a: to 100%

**Control 2:**

The formulation was prepared as described in the preparation paragraph, with the following concentrations:

Beclomethasone dipropionate: 0.2%

HFA-227ea: to 100%

**Control 3:**

Microparticles of salbutamol sulphate were prepared by spray drying from an aqueous solution, using a Büchi 190 mini spray drier fitted with a 7 mm pneumatic nozzle. A 10%

APGs in HFA-134a) are not as good as the control (Control 3) . However after one month's storage, the Control has deteriorated but the suspensions formulated with APGs have improved significantly.

Sample 7 (salbutamol sulphate with APG in HFA-134a) is to be compared with control 7.

- 5 Again, the presence of the APG improves suspension stability by increasing the creaming times, with a particularly beneficial influence after storage.

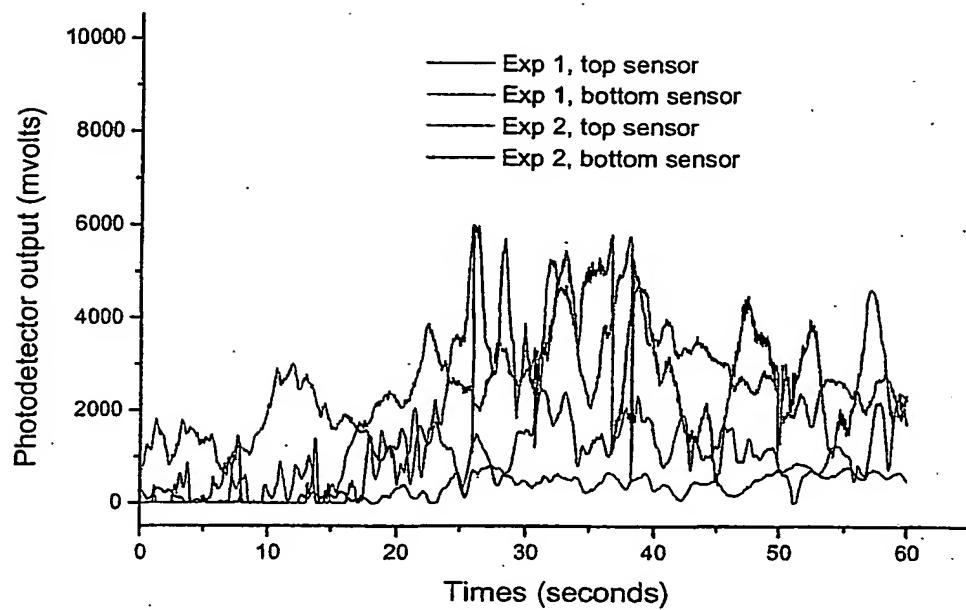


Figure 1 Example 1, BDP+C<sub>12</sub>G<sub>2</sub> in HFA-134a

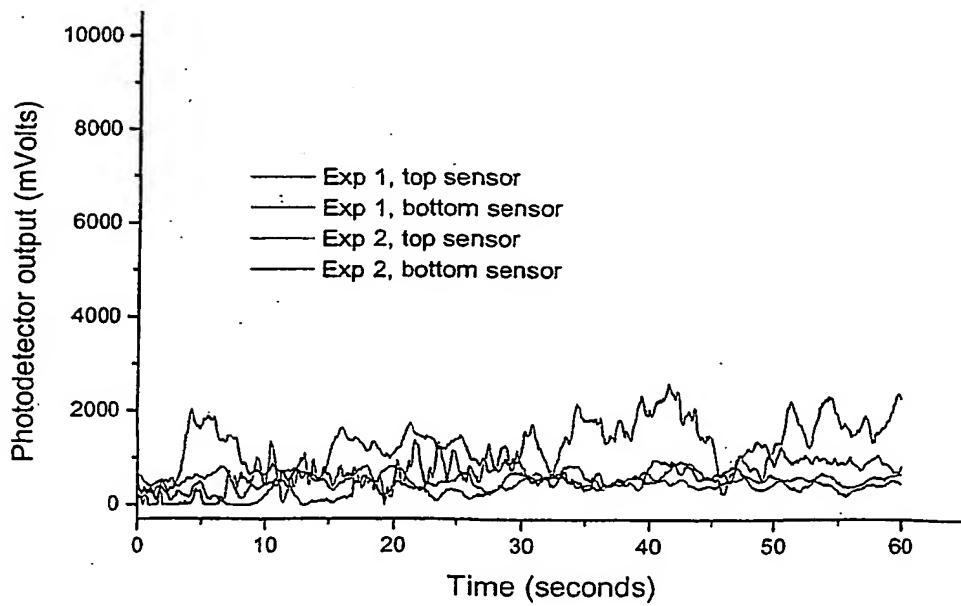
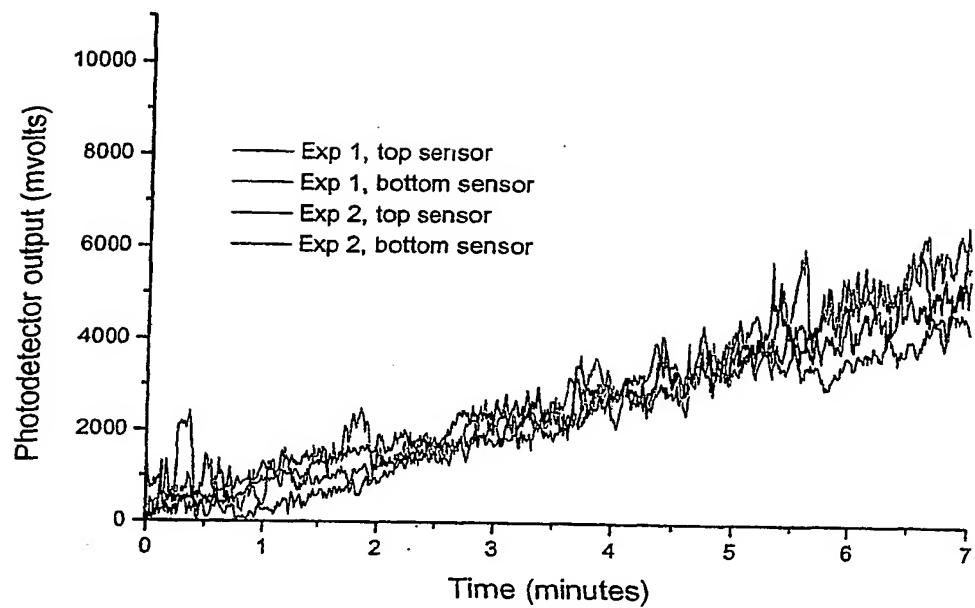
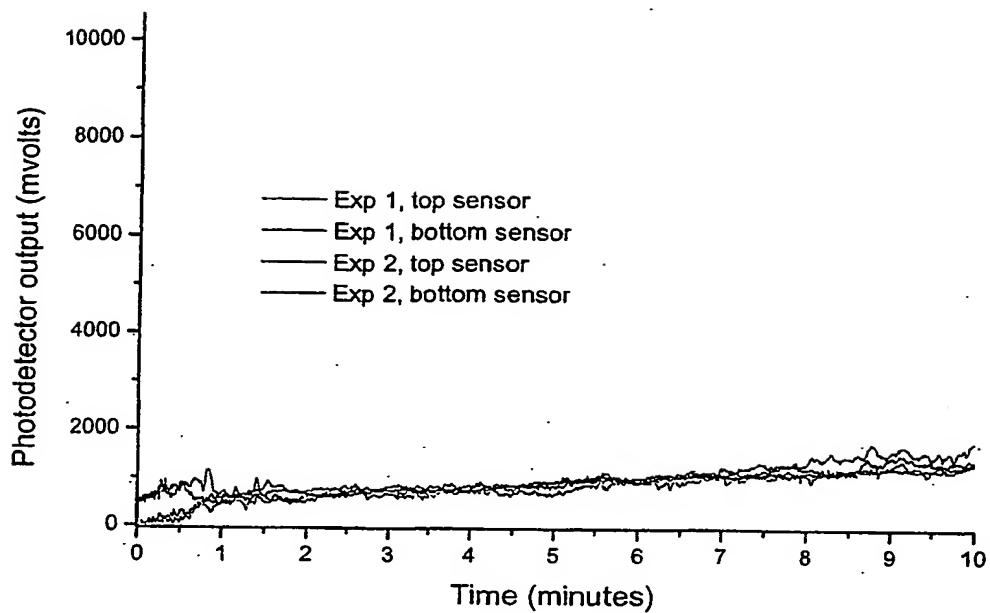


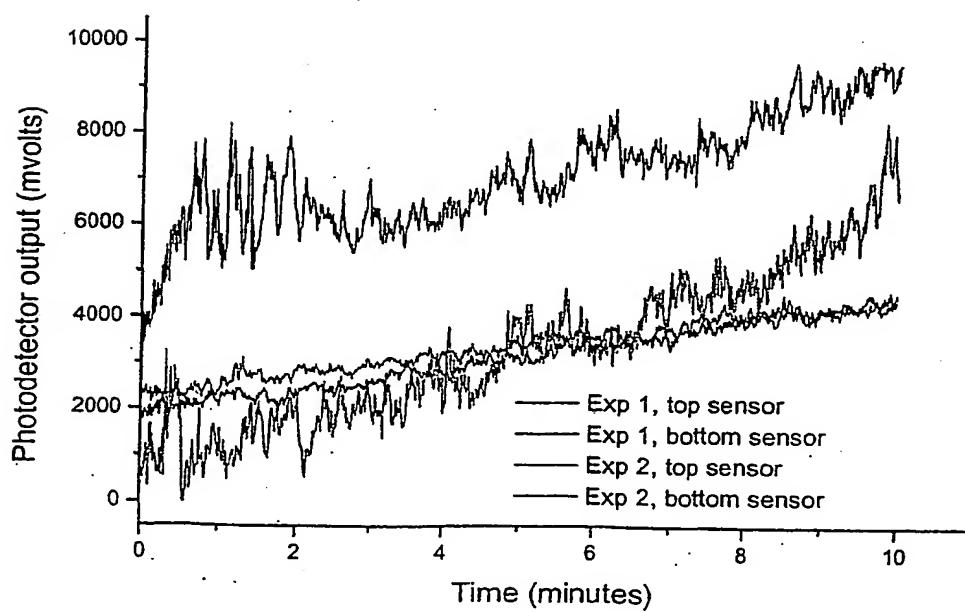
Figure 2 Example 2, BDP + C<sub>12</sub>G<sub>2</sub> in HFA-227ea



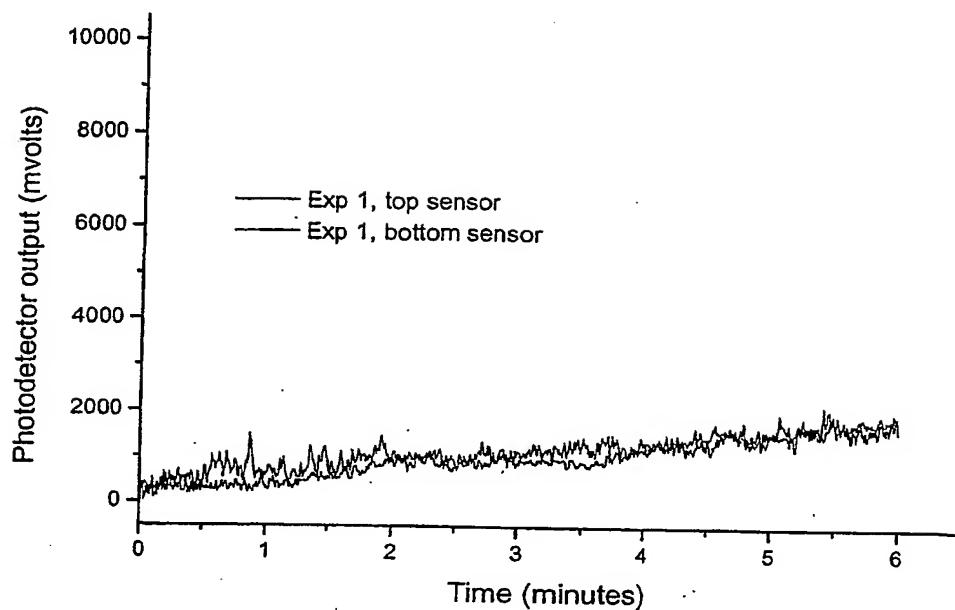
**Figure 3 Example 3, BDP +C<sub>10-12</sub> d.p.: 1.4 in HFA-134a**



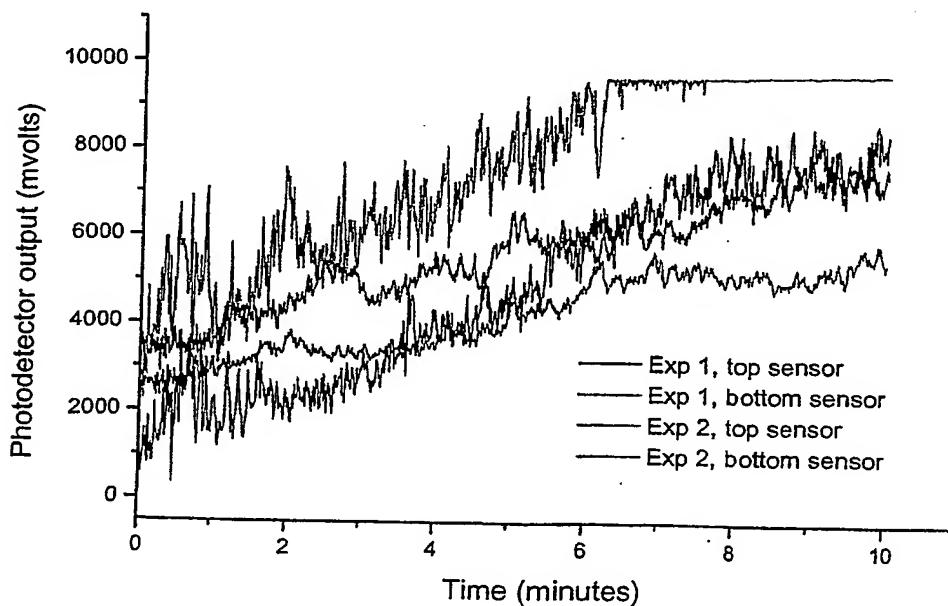
**Figure 4** Example 4, BDP+C<sub>10-12</sub> d.p. 1.4 in HFA-227ea



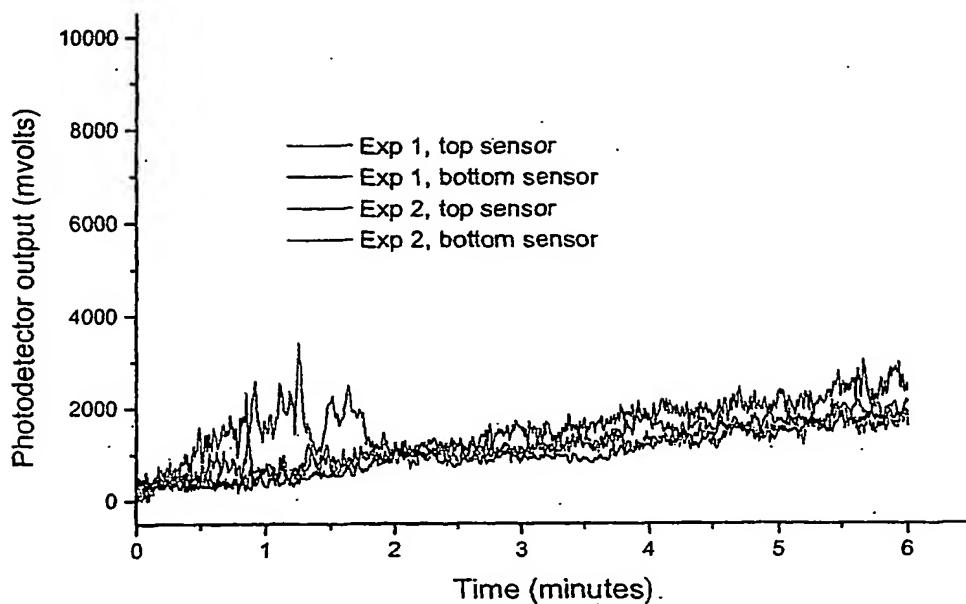
**Figure 5.1** Example 5, SD salbutamol sulphate + C<sub>12-14</sub>  
d.p. 1.4 in HFA-134a



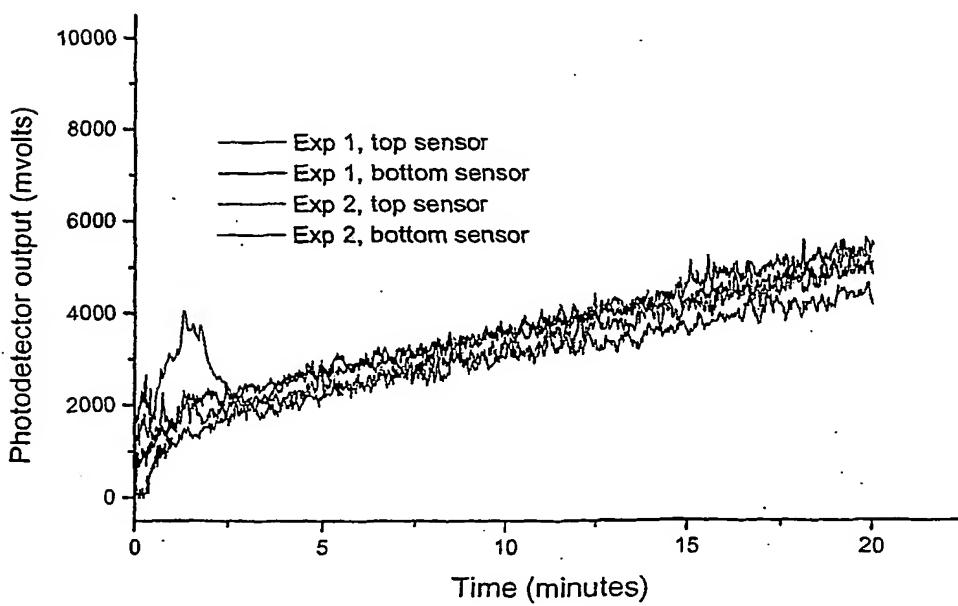
**Figure 5.2** Example 5, SD salbutamol sulphate + C<sub>12-14</sub> d.p. 1.4 in HFA-134a, 1 month stability study



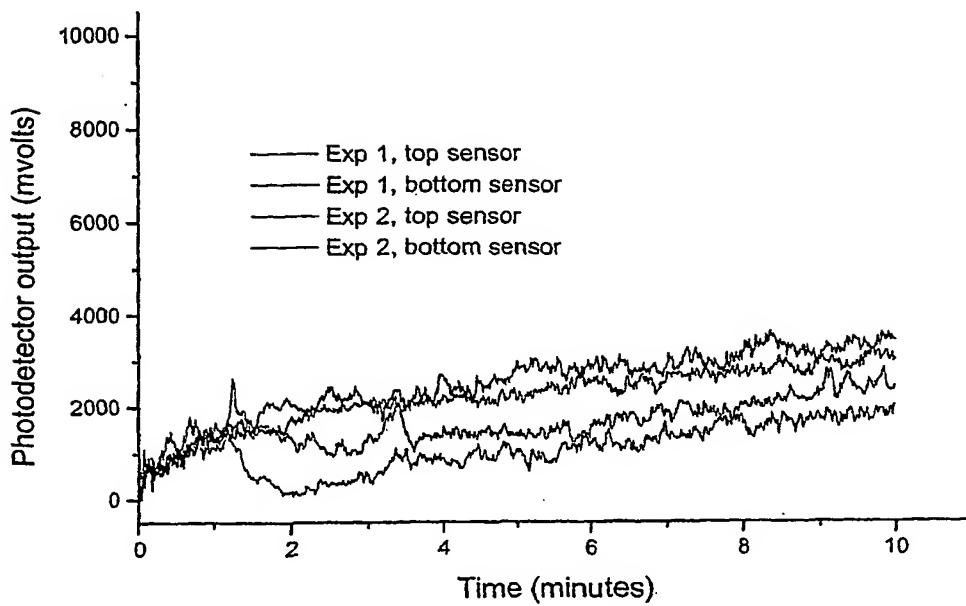
**Figure 6.1** Example 6, SD salbutamol sulphate + C<sub>12</sub>G<sub>2</sub> in HFA-134a



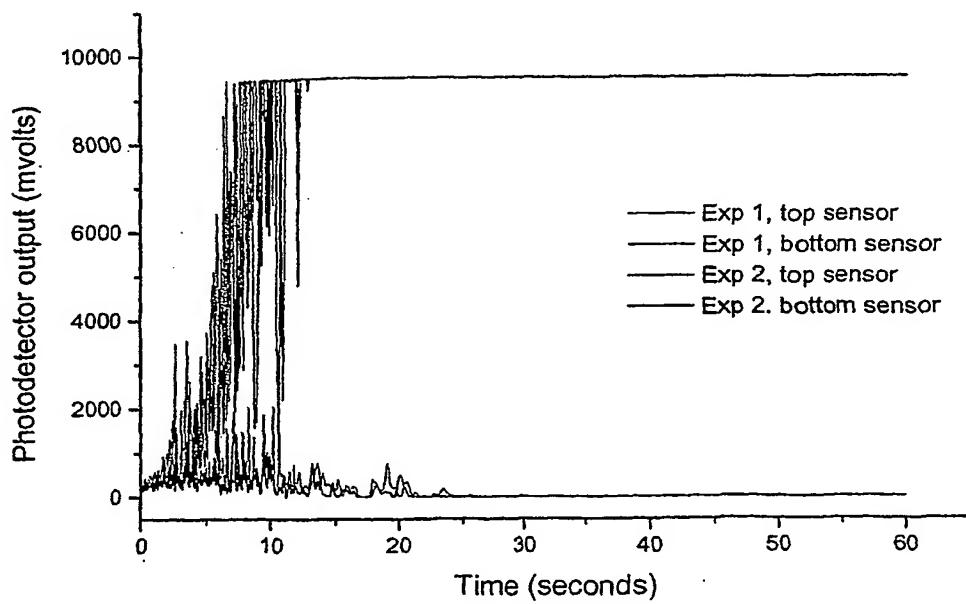
**Figure 6.2 Example 6, SD salbutamol sulphate + C<sub>12</sub>G<sub>2</sub> in HFA-134a, 1 month stability study**



**Figure 7.1 Example 7, Salbutamol sulphate + C<sub>14</sub> d.p. 1.4 in HFA-134a**



**Figure 7.2** Example 7, Salbutamol sulphate + C<sub>14</sub> d.p. 1.4 in HFA-134a, 1 month stability



**Figure 8** Control 1, BDP in HFA-134a

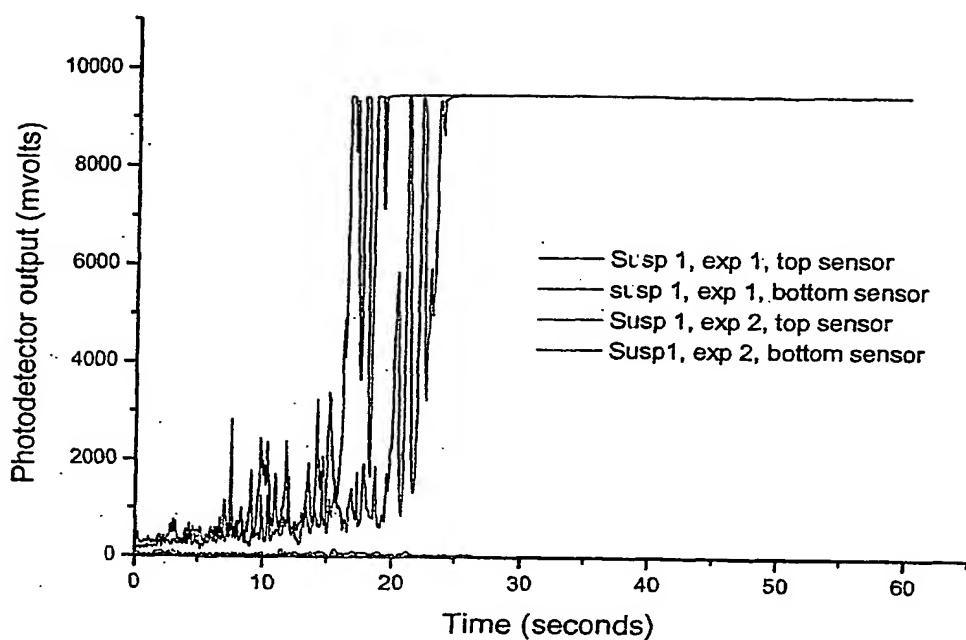
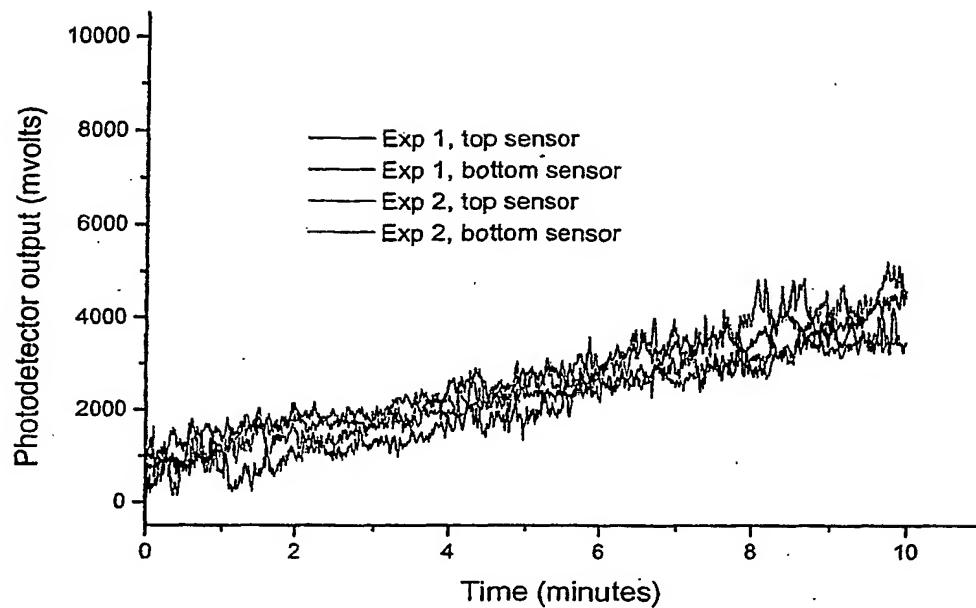
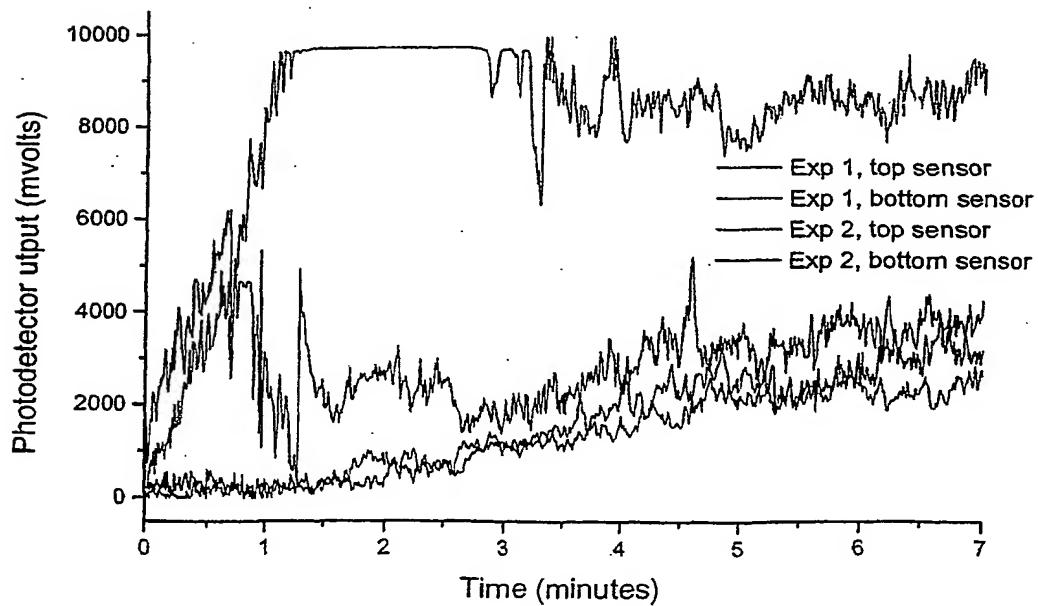


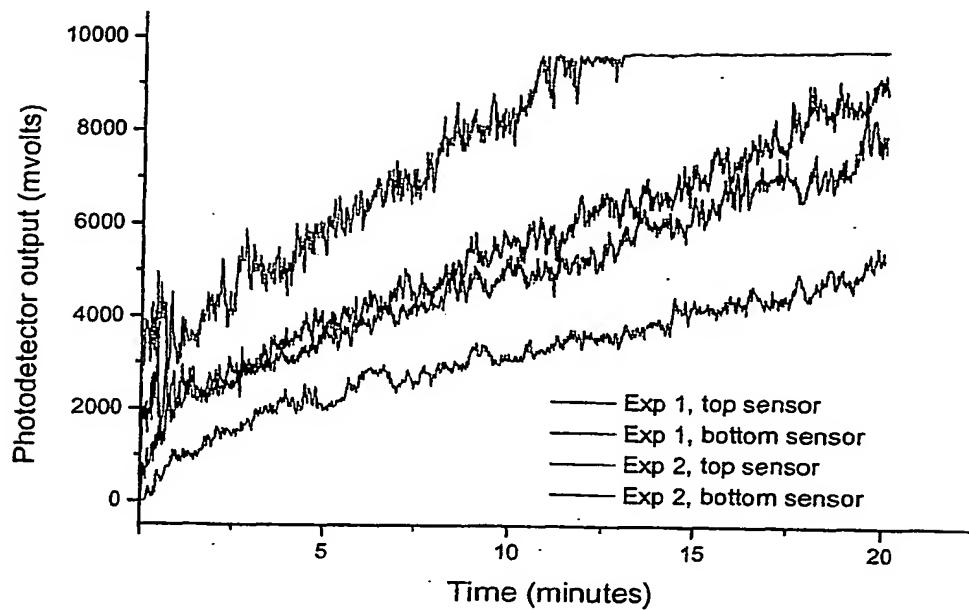
Figure 9 Control 2, BDP in HFA-227ea



**Figure 10** Control 3, Spray dried salbutamol sulphate in  
HFA-134a

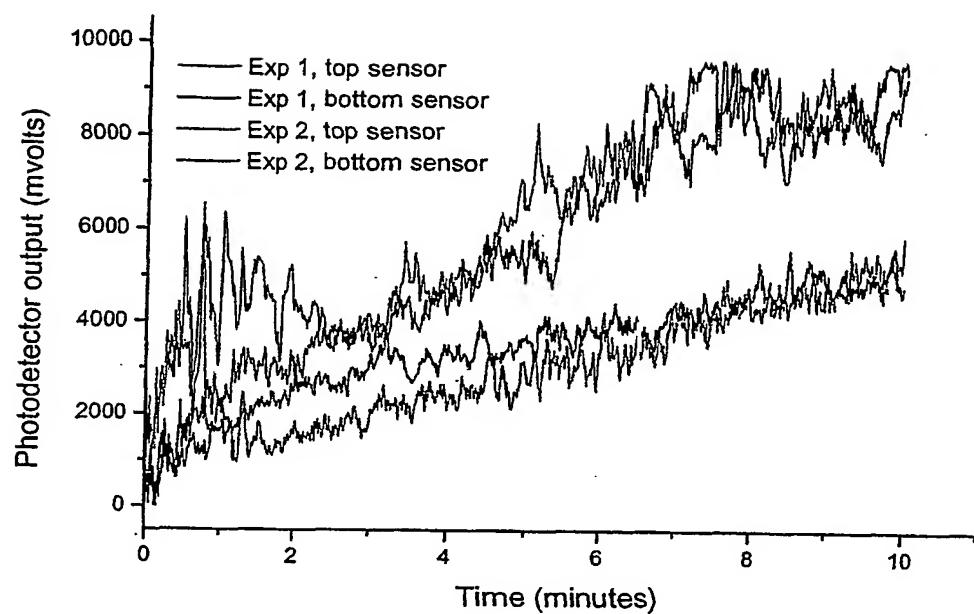


**Figure 11** Control 3, Spray dried salbutamol sulphate in HFA-134a, 1 month  
stability study



igure 12.1 Control 4, Salbutamol sulphate in HFA-

134a



**Figure 12.2 Control 4, Salbutamol sulphate in HFA-134a,  
1 month stability**

### Visual Assessment

Visual assessment was carried out on the OSCAR samples. After removing the samples from the ultrasonic bath, observations were made to assess the degree of flocculation of the drug suspensions and also the kinetics of sedimentation or creaming.

Sample	Material	HFA	Flocculation ?	Sedimentation /creaming
1	BDP + C <sub>12</sub> G <sub>2</sub>	134a	No	Slow
2	BDP + C <sub>12</sub> G <sub>2</sub>	227ea	No	Slow
3	BDP + C <sub>10-12</sub> d.p.1.4	134a	No	Very slow
4	BDP + C <sub>10-12</sub> d.p.1.4	227ea	No	Very slow
5	SD salbutamol sulphate + C <sub>12-14</sub> d.p. 1.4	134a	Yes	Fast
6	SD salbutamol sulphate + C <sub>12</sub> G <sub>2</sub>	134a	Yes	Fast
7	Salbutamol sulphate + C <sub>14</sub> d.p. 1.4	134a	No	Very slow
Control 1	BDP	134a	Yes	Very fast
Control 2	BDP	227ea	Yes	Very fast
Control 3	SD salbutamol sulphate	134a	Yes	Slow
Control 4	Salbutamol sulphate	134a	Yes	Fast

For all systems, the presence of APG improved the suspension characteristics. Initial observations are summarised in the previous table. After one month storage, the spray dried salbutamol samples showed a definite improvement compared to the control samples (Control 3).

One month stability:

Sample	Material	HFA	Flocculation ?	Sedimentation /creaming
5	SD salbutamol sulphate + C <sub>12-14</sub> d.p. 1.4	134a	Yes	slow
6	SD salbutamol sulphate + C <sub>12</sub> G <sub>2</sub>	134a	Yes	Slow
Control 3	SD salbutamol sulphate	134a	Yes	Fast

5 IGC

Surface energy of the drug and the drug surfactant particles was measured by inverse gas chromatography. A silanised U-shaped column (3 mm internal diameter, 30 cm length) was packed with approximately 400 mg of the test powder and dried under nitrogen for 24 hours at 50°C. The powder bed was then allowed to settle for 24 hours at 35°C (temperature used during the experiments) under nitrogen. The test probes used were: hexane, heptane, octane, chloroform, CCl<sub>4</sub>, benzene, acetone, tetrahydrofuran, ethyl acetate and diethyl ether. One ml of air containing a minute concentration of each gaseous probe was injected into the column and the retention time measured.

15

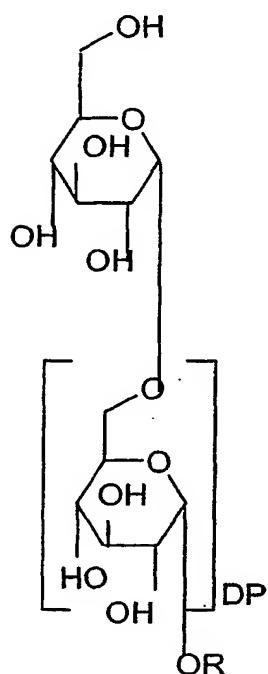
The APG reduced the surface energy of the particles notably (not for the SD material?). I think we should remove the SD material & results. The improved suspension characteristics can therefore be attributed to surface modifications.

MATERIAL	$\gamma_s^D$ MJ/M <sup>2</sup> (n=3)	Kd/Ka
BDP	52.34 ( 1.09)	8.82
BDP + C <sub>12</sub> G <sub>2</sub>	50.25 (1.33)	6.09
BDP + C <sub>10-12</sub> d.p. 1.4	36.30 (1.62)	2.15
Salbutamol sulphate	43.27 (0.67)	1.76
Salbutamol sulphate + C <sub>14</sub> d.p. 1.4	38.23 (0.36)	2.61

Think we should remove this as the density did change for APG material & the conclusion doesn't match the data.

## CLAIMS

1. A pharmaceutical aerosol formulation comprising a hydrofluoroalkane propellant, a medicament for inhalation and a surfactant, characterised in that the surfactant is an alkyl-polyglycoside of formula I:



wherein DP is the average degree of polymerisation and has a value of from 1 to 4, and R is an alkyl chain or a mixture of alkyl chains having a chain length of from 6 to 22 carbon atoms; or a derivative thereof.

2. A formulation according to claim 1 in which  
R is 2-ethyl-1-hexylglycoside and DP is 1.6;  
R is a mixture of C<sub>8</sub> and C<sub>10</sub> alkyl chains in a ratio of 60 C<sub>8</sub> : 40 C<sub>10</sub> and DP is 1.5;  
R is a mixture of C<sub>16</sub> and C<sub>8</sub> alkyl chains and DP is 1.2 - 1.3; or  
R is a mixture of C<sub>20</sub> and C<sub>22</sub> alkyl chains and DP is 1.2 - 1.3, or the alkylpolyglycoside is n-dodecyl β-D-maltoside (C<sub>12</sub>G<sub>2</sub>), C<sub>10</sub> d.p. 2.7, or C<sub>10-12</sub> d.p. 1.4 and C<sub>12-14</sub> d.p.
3. A formulation according to claim 1 or 2 in which the propellant is HFA-134a or HFA-227ea or mixtures thereof.

4. A formulation according to any one of claims 1 to 3 in which the medicament is a  $\beta$ 2-adrenoreceptor agonist; an anticholinergic bronchodilators or a 16, 17-acetal of a pregnane derivative.
5. A formulation according to any one of claims 1 to 3 in which the medicament is formoterol, terbutaline, budesonide or a formoterol/budesonide combination.
6. A formulation according to any one of claims 1 to 3 in which the medicament is a compound of formula (I):

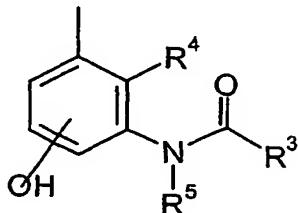
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in which

Ar represents a group

15



A represents a C<sub>1-12</sub> alkylene chain which may be straight or branched and which is interrupted or terminated by one or more groups selected from -S-, -SO-, SO<sub>2</sub>-, -O-, SO<sub>2</sub>NH, NHSO<sub>2</sub>, CR<sup>6</sup>R<sup>7</sup>, phenylmethyne, -NH-, -CONH-, -NHCO- and -NHCONH-;

Z represents an aryl group of five or six atoms in a single ring system, which may contain from 1 to 3 heteroatoms selected from N, O and S, which single ring system may be optionally substituted to form a multiple fused ring system of up to 10 atoms, the aryl group being optionally substituted by one or more groups selected from -OH, halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, =O, -NR<sup>8</sup>R<sup>9</sup>, or NO<sub>2</sub>; or a C<sub>3-12</sub> cycloalkyl group which may contain from 1 to 3 heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from -OH, halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, =O, -NH<sub>2</sub>, or NO<sub>2</sub>;

20 R<sup>1</sup>, R<sup>2</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> each independently represent hydrogen or C<sub>1-6</sub> alkyl;

25 and

R<sup>3</sup> and R<sup>4</sup> represent hydrogen, or R<sup>3</sup> and R<sup>4</sup> together form a group -S-, -NR<sup>8</sup>- or -CH<sub>2</sub>-, and pharmaceutically acceptable derivatives thereof.

- 30 7. A formulation according to any one of claims 1 to 3 in which the medicament is

4-Hydroxy-7-[2-[2-[3-(2-phenylethoxy)propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3H)-one;

4-Hydroxy-7-[2-[2-[3-(2-phenylethoxy)propoxy]ethylamino]ethyl]-1,3-benzothiazol-2(3H)-one;

5 N-[2-[2-(4-Hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]ethyl]-2-(phenylethoxy)ethanesulphonamide;

4-Hydroxy-7-[2-[3-[2-[2-(1-naphthalenyl)ethoxy]ethylsulphonyl]propylamino]ethyl]-1,3-benzothiazol-2(3H)-one; and

10 3-[2-(4-Hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[4-methylphenyl]ethoxy]ethyl]propanesulphonamide,  
and pharmaceutically acceptable salts thereof.

8. A formulation according to any one of claims 1 to 3 in which the medicament is a combination of formoterol/budesonide; formoterol/fluticasone; formoterol/mometasone;  
15 salmeterol/fluticasone; formoterol/tiotropium salts; zafirlukast/formoterol, zafirlukast/budesonide; montelukast/formoterol; montelukast/budesonide; loratadine/montelukast and loratadine/zafirlukast, tiotropium and fluticasone, tiotropium and budesonide, tiotropium and mometasone, mometasone and salmeterol, formoterol and rofleponide, salmeterol and budesonide, salmeterol and rofleponide, or tiotropium and rofleponide.  
20

9. A formulation according to any one of claims 1 to 8 in which the amount of surfactant present is at least 0.001% by weight.

25 10. A formulation according to any one of claims 1 to 9 in which the amount of medicament present is from 0.01 to 1.0% by weight.

11. A medicinal aerosol containing a formulation according to any one of claims 1 to 10.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 01/02853

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/12, A61K 47/26

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9619198 A1 (ASTRA AKTIEBOLAG), 27 June 1996 (27.06.96)  --	1-11
A	STN International, File CAPLUS, CAPLUS accession no. 1997:328726, Document no. 126:306557, Chuo Eazooru Kagaku Kk: "Alkyl glucoside-based aerosol-type foam products"; & JP,A2,09059606, 19970304  --	1-11
A	WO 9830244 A1 (MINNESOTA MINING AND MANUFACTURING COMPANY), 16 July 1998 (16.07.98), page 16, line 17 - page 17, line 7  --	1-11

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	
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Date of mailing of the international search report

12 March 2002

20 -03- 2002

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## INTERNATIONAL SEARCH REPORT

International application No.  
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A	WO 9500151 A1 (UAB RESEARCHFOUNDATION), 5 January 1995 (05.01.95), page 8, line 20 - page 9, line 7; page 11, line 1 - line 5; page 12, line 13 - line 16; page 15, line 19 - line 24; the claims  --	1-11
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